

CHIRAL PHOSPHORATED LIGANDS USEFUL IN CATALYSTS**Scope of invention**

The present invention refers to new atropo-isomeric chiral phosphorated ligands having C_1 symmetry, the procedure for their preparation, the organometallic complexes containing said phosphorated ligands in optically active form, and the use of these complexes as catalysts in stereoselective organic syntheses.

Prior art

Stereoselective reactions catalysed by enantiomerically pure complexes of transition metals, such as enantio- and/or diastereo-selective reactions of reduction, isomerization, hydroformylation, hydroboration, hydrosilylation, hydrocyanation, allylation, vinylation, and other reactions of formation of the C-C bond, are the subject of considerable interest from the scientific and application standpoints.

The patent application WO 96/01831 describes chiral diphosphines consisting of a C_2 -symmetry atropo-isomeric biheterocyclic pentatomic aromatic system, which, by complexation with transition metals, give rise to chiral catalysts capable of inducing good stereoselection in enantio- and/or diastereo-selective reduction and isomerization reactions.

Technical problem

For the use on an industrial scale of chiral organometallic catalysts, in addition to the stereoselectivity induced by these catalysts, of great importance are factors such as their cost, stability, productivity (kg of product per kg of catalyst per day), and the possibility of efficient recycling in the absence of racemization and loss of stereoselection. In addition, there does not exist a catalyst which is suitable for any reaction, nor, given the same reaction, for any substrate.

For example, even though the catalysts containing C_2 -symmetry atropo-isomeric biheterocyclic ligands described by WO 96/01831 are endowed with a good capacity for inducing stereoselection in the reactions referred to above, they prove less efficient in certain stereoselective reactions, such as hydroformylation, hydrocyanation or hydrosilylation.

Consequently, even though the number of organometallic catalysts is high and constantly increasing, the need is felt for identifying new chiral catalysts that are selective, easy to prepare, economical, stable, provided with high productivity, and may be possibly recycled without racemizing and without losing stereoselectivity.

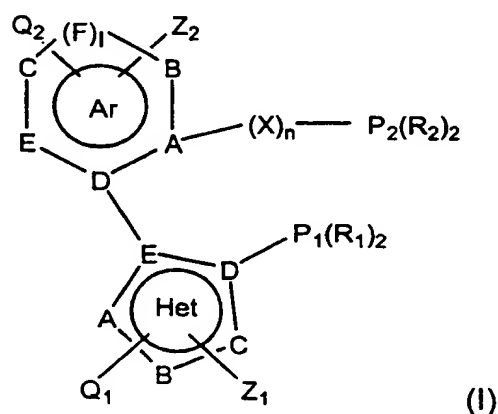
- 5 The search for new and efficient asymmetric catalysts is still based upon the synthesis and experimental verification of a large number of compounds.

Even though an approach of this kind may be fruitful in some cases, it entails numerous disadvantages in terms of work and costs, and often leads to unsatisfactory results.

10 Summary

- Now the applicant has unexpectedly found a critical selection of molecular parameters which enables the properties of phosphorated ligands to be foreseen, and hence selective and efficient organometallic catalysts to be synthesized, determining *a priori* the structures of interest, and thus avoiding a purely
 15 experimental approach based upon the synthesis and *a posteriori* verification of the properties of the ligands.

- A fundamental feature of the present invention hence consists in atropo-isomeric chiral phosphorated ligands of formula (I), having C_1 symmetry, in the optically active form or in the racemic form, i.e., as individual atropo-isomers or mixtures of
 20 these :



wherein

- 25 the atoms A, B, C, D, E and F, which are equal to or different from one another,

are carbon atoms or hetero-atoms chosen from among oxygen, nitrogen and sulphur, which form together an Ar of Het aromatic residue, where Ar is chosen between pentatomic heterocyclic residue and phenyl, and Het is a pentatomic heterocyclic residue, and where said pentatomic heterocyclic aromatic residue
5 contains 1 or 2 hetero-atoms, equal to or different from one another, selected from the group consisting of -O-, -S- and -NR₃-, wherein R₃ = H, an alkyl group (for example, C₁-C₆), an aromatic group (for example, phenyl), a group -P₁(R₁)₂, or a nitrogen atom comprised as hetero-atom in the other pentatomic heterocyclic residue belonging to the structure of formula (I) ;

10 I = 0, 1 ; when I = 1, F is a carbon atom ;

R₁ and R₂, bound to the phosphorous atoms, equal to or different from one another, are selected from a linear, branched or cyclic C₃-C₁₀ alkyl group, a carbocyclic aromatic group (for example, phenyl or naphthyl), and a heterocyclic aromatic group having 5-6 members in the cycle, containing one or more hetero-
15 atoms (for example, 1-2) chosen among oxygen, sulphur and nitrogen, where said carbocyclic or heterocyclic aromatic group is possibly substituted with one or more groups selected from a linear or branched C₁-C₁₀ alkyl group, a linear or branched C₁-C₁₀ alkoxyl group, an halogen, -COOR₄, -SO₃R₄ and -NR₅R₆, where R₄ is chosen among H, alkyl (for example, C₁-C₁₀), aryl (for example, phenyl), alkaline or
20 alkaline-earth metal, -NH₄⁺ and alkyl ammonium cation having from 4 to 20 carbon atoms ; and where R₅ and R₆, equal to or different from one another, are H or alkyl (for example, C₁-C₁₀ alkyl) ; or

R₁ together with the phosphorous atom, or R₂ together with the phosphorus atom, form a heterocycle having 3-6 atoms in the cycle, possibly substituted with
25 linear or branched C₁-C₁₀ alkyl groups ;

X is an -O- group or an -N(R₇)- group, where R₇ is chosen among H, alkyl (for example, C₁-C₆ alkyl) and phenyl ;

n may have one of the following values :

is 0 or 1, when Ar is a heterocyclic aromatic residue, and

30 n is 1, when Ar is phenyl ;

Q_1 , Q_2 , Z_1 and Z_2 , equal to or different from one another, are selected from the group consisting of H, linear, branched or cyclic C_1 - C_{10} alkyl, linear or branched C_1 - C_{10} alkoxy, a carbocyclic aromatic residue (for example, phenyl) and halogen, or

- 5 Q_1 taken together with Z_1 , or Q_2 taken together with Z_2 , form a carbocyclic aromatic ring (for example, phenyl or naphthyl), possibly substituted with one or more T groups (for example, one or two T groups), where T is chosen among halogen, C_1 - C_{10} alkyl, C_1 - C_{10} alkoxyl, $-\text{COOR}_4$, $-\text{SO}_3\text{R}_4$ and $-\text{NR}_5\text{R}_6$, where R_4 is selected from H, alkyl (for example, C_1 - C_{10} alkyl), aryl (for example, phenyl),
 10 alkaline or alkaline-earth metal, $-\text{NH}_4^+$ or alkyl ammonium cation having from 4 to 12 carbon atoms, and where R_5 and R_6 , equal to or different from one another, are selected from H and alkyl (for example, C_1 - C_{10} alkyl).

The groups $-\text{P}_1(\text{R}_1)_2$ and $-(\text{X})_n-\text{P}_2(\text{R}_2)_2$ are bound to the corresponding carbocyclic or heterocyclic aromatic residue by means of a carbon atom of said aromatic
 15 residue or by means of a nitrogen atom comprised as hetero-atom in a pentatomic heterocyclic residue.

The ligands in question moreover present:

- i) a difference between the residual charges of the phosphorous atoms

$$\Delta Q(\text{P}) = Q(\text{P}_1) - Q(\text{P}_2) > 0.05 \quad (\text{preferably} > 0.15),$$

- 20 where $Q(\text{P}_1)$ and $Q(\text{P}_2)$ are the values of difference between the number of valence electrons and the number of electrons actually present for the phosphorous atoms P_1 and P_2 ;

- ii) a cone angle β_n ("natural bite angle" according to Casey), ranging from 80° to 130° , preferably from 83° to 120° , defined as preferred chelation angle $\text{P}_1\text{-M-P}_2$,
 25 between the phosphorous atoms P_1 and P_2 and a transition metal M, obtained by minimization of the strain energy of the fragment $\text{M}(\text{diphosphine})$, choosing Rh as transition metal;

- iii) a value of the barrier of interconversion energy between the two enantiomers of a given ligand

30
$$\Delta E = E_{\text{trans}} - E_{\text{min}} \geq 28 \text{ Kcal/mol},$$

where E_{trans} is the energy value for the transition state, and E_{min} is the energy value for the state of minimum energy of the enantiomers, expressed in Kcal/mol.

A further subject of the present invention is the procedure of preparation of the above-mentioned ligands of formula (I), comprising:

- 5 a) construction of the molecular model of a series of structures of ligands of formula (I) as defined above, indicated as $(I)_1$, $(I)_2$, $(I)_3$, ..., $(I)_z$, where z is the number of structures created, carried out by using the computation program SYBYL, Version 6.2;
- b) conformational analysis, comprising the determination, for each structure from
10 $(I)_1$ to $(I)_z$, of the minimum-energy conformer, followed by optimisation using the program MOPAC, Version 6.0, Method MNDO;
- c) calculation, for each minimum-energy conformer structure, of the above defined difference

$$\Delta Q(P) = Q(P_1) - Q(P_2),$$

- 15 by using the computation program MOPAC, Version 6.0, Method MNDO;
- d) calculation, for each structure from $(I)_1$ to $(I)_z$, of the value of the above defined interconversion energy barrier between the two enantiomers (atropo-isomers) of formula (I)

$$\Delta E = E_{\text{trans}} - E_{\text{min}},$$

- 20 by means of the computation program MOPAC, Version 6.0, Method MNDO, imposing that the value E_{trans} should be that of the maximum-energy conformer having the two rings Ar and Het of the structure (I) coplanar with respect to one another;
- e) calculation, for each structure from $(I)_1$ to $(I)_z$, of the natural bite angle β_n , as
25 defined above, obtained by minimization of the strain energy of the fragment M(diphosphine), imposing that M should be Rh and that the bending constant of the bond $P_1\text{-M-P}_2$ should be 0 Kcal/mol, and calculated by using the program SYBYL, Version 6.2, and adopting the parameters of the force field of the program TRIPOS, modified by entering the parameters developed for the Rh-diphosphine
30 complexes by M. Kranenburg et al. [Organometallics, 14, 3081, 1995];
- f) selection of the structures from $(I)_1$ to $(I)_n$ having:

i) $\Delta Q(P) = Q(P_1) - Q(P_2) > 0.05$ (preferably > 0.15) ;

ii) a cone angle β_n ranging from 80° and 130° (preferably between 83° and 120°) ;

5 iii) an interconversion energy barrier between the two enantiomers of one and the same structure $\Delta E \geq 28$ Kcal/mol ;

g) chemical synthesis of the phosphorated ligands of formula (I) thus selected.

The structure of the compounds of formula (I) in which n is 1, and X is -O- or -NR₇ has been identified by setting by approximation that



10 i.e., that the phosphorous atom P₂ is directly bound to a tetrahedral carbon atom C.3, instead of to oxygen or nitrogen, and hence by using for the bonds N-P₂ and O-P₂ the same calculation parameters as those used for the bond C.3 - P₂ .

Once resolved into their optical antipodes, the present atropo-isomeric chiral phosphorated ligands of formula (I), having C₁ symmetry, are useful in the
15 preparation of complexes with transition metals, which are in turn useful as catalysts in stereoselective reactions.

Further aspects of the present invention are therefore represented by the organometallic complexes between the optically active form (enanatiomerically pure or at least enriched) of a ligand of formula (I) and a transition metal, the
20 procedure for their preparation, and their use in the preparation of an optically active chiral catalyst. Further subjects of the present invention are the use of the present catalyst in stereoselective (diastereoselective or enantioselective) reactions, and therefore the processes of synthesis for the preparation of organic compounds in the form of stereo-isomers, which comprise at least one
25 stereoccontrolled reaction carried out in the presence of one of the present optically active chiral catalysts.

The optically active chiral catalysts of the present invention have unexpectedly been found to be superior to those described by WO 96/01831 in some stereoselective reactions.

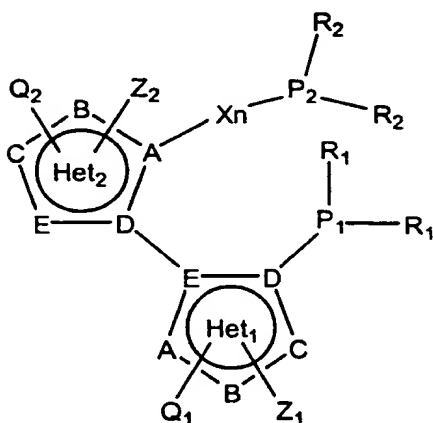
30 **Brief description of the figures**

Figures 1-3 show the structures of some examples of phosphorated ligands according to the present invention, indicated as compounds (1) - (15).

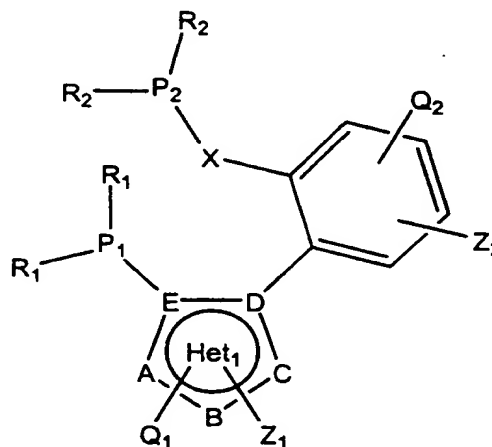
Detailed description

In the phosphorated ligands of the present invention, the atoms engaged in the bond between the two aromatic cycles are carbon atoms or nitrogen atoms.

The present ligands of formula (I) having C_1 symmetry in which Ar is a heterocycle and those in which Ar is phenyl are represented by the following formulas (I)a and (I)b, respectively :



(I)a



(I)b

wherein

Het₁ and Het₂ are pentatomic heterocyclic aromatic rings, equal to or different from one another, defined as Het is defined above ;

n is 0 or 1; and

X, A, B, C, D, E, Q₁, Q₂, Z₁ and Z₂ are as defined above.

The condition that the above-mentioned ligands should have C_1 symmetry imposes that the two substituted aromatic residues present in formula (I) are not mutually specular. Hence, in the case of the ligands of formula (I)a, at least one of the following requirements must be met :

R₁ ≠ R₂,

Het₁ ≠ Het₂,

Q₁ ≠ Q₂,

Z₁ ≠ Z₂, or

n = 1.

In the case where $\text{Het}_1 = \text{Het}_2$, $R_1 = R_2$, $Q_1 = Q_2$, $Z_1 = Z_2$, and $n = 0$, the C_1 -type asymmetry occurs, for example, when the two pentatomic cyclic residues, even if they derive from the same type of aromatic heterocycle, are bound together via two different relative positions with respect to the hetero-atom, for example via the position 2' of Het_1 and the position 3' of Het_2 .

Examples of Het , Het_1 and Het_2 heterocyclic residues are thiophene, pyrrole, furan, imidazole, isoxazole, isothiazole, pyrazole and triazole.

When the substituents Q_1 and Z_1 taken together, or Q_2 and Z_2 taken together, form a carbocyclic aromatic ring, the Het , Het_1 or Het_2 pentatomic heterocyclic ring is condensed with phenyl or naphthyl. In this case Het , Het_1 or Het_2 may be, for example, benzothiophene, naphthothiophene, indole, benzofuran or benzoimidazole.

Q_1 , Q_2 , Z_1 and Z_2 are, for example, methyl.

Examples of heterocyclic aromatic residues present in the ligands of the present invention are 2,5-dimethyl-thien-3-yl, 4,6-dimethyl-benzofur-3-yl, 3-methyl-indol-2-yl, 1-N-methyl-indol-2-yl and benzothien-3-yl.

The carbocyclic aromatic residue is, for example, phenyl.

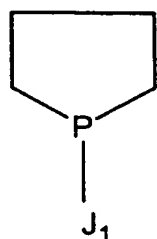
n is, for example, 0.

When $n = 1$, X is, for example, $-\text{O}-$.

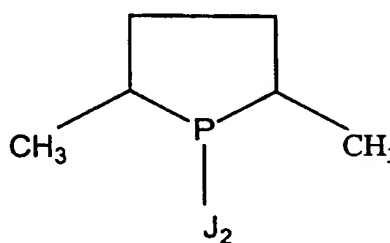
For example, in certain compounds $\text{Ar} = \text{phenyl}$, $n = 1$ and $X = -\text{O}-$.

The groups R_1 and R_2 are, for example, phenyl or cyclohexyl, hence $-\text{P}_1(\text{R}_1)_2$ and $-\text{P}_2(\text{R}_2)_2$ are, for instance, diphenyl phosphine or dicyclohexyl phosphine.

According to other embodiments of the present invention, the two R_1 residues bound together with the atom P_1 (or the two R_2 residues bound together with the atoms P_2) represent a cyclic residue J_1 or J_2 .

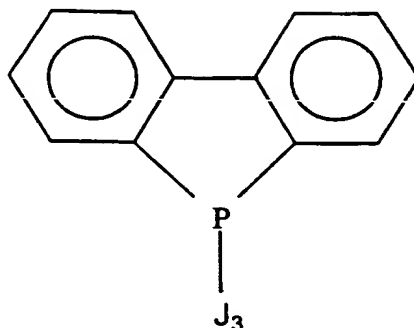


(phospholyl)



(2',5'-dimethyl-phospholyl)

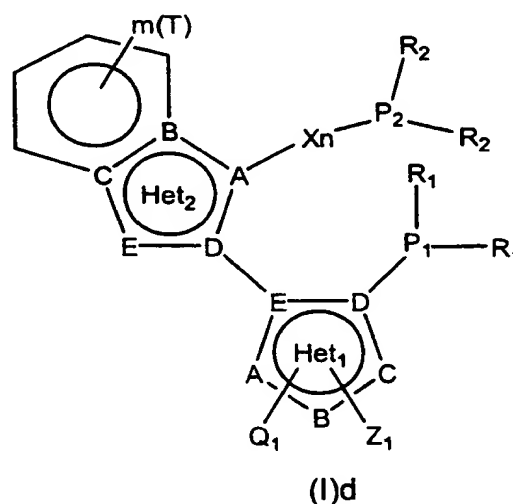
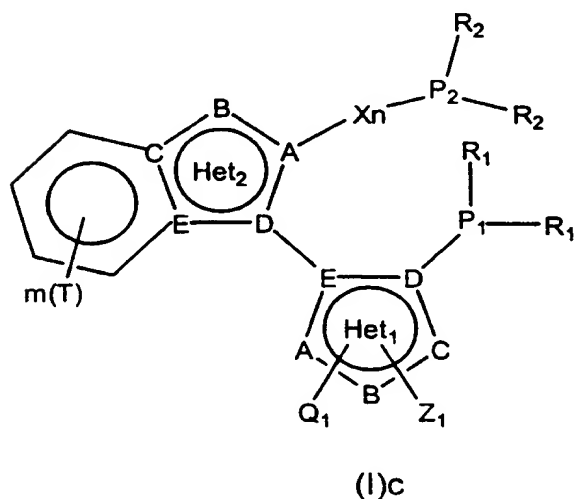
or a polycyclic aromatic residue, for example, of formula J₃

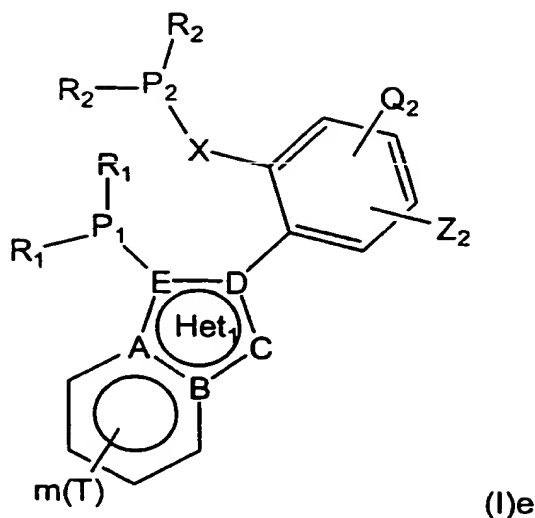


(dibenzophospholyl)

- 5 Examples of sub-structures contained in the phosphorated ligands of the present invention are: (4-diphenylphosphine)- or (4-dicyclohexylphosphine)-2,5-dimethyl-thien-3-yl; (1-N-diphenylphosphine)- or (1-N-dicyclohexylphosphine)-3-methylindol-2-yl; (3-diphenylphosphine)- or (3-dicyclohexylphosphine)-1-N-methylindol-2-yl; 2-(diphenylphosphine)- or 2-(dicyclohexylphosphine)-benzothien-3-yl; 2-(diphenylphosphine-oxy)- or 2-(dicyclohexylphosphine-oxy)-phenyl-1-yl; 4-(diphenylphosphine-oxy)- or 4-(dicyclohexylphosphine-oxy)-2,5-dimethyl-thien-3-yl; 4-(2',5'-dimethyl-phospholyl)- or 4-(dibenzophospholyl)-2,5-dimethyl-thien-3-yl; 1-N-(2',5'-dimethyl-phospholyl)- or 1-N-(dibenzophospholyl)-3-methyl-indol-2-yl.

15 Examples of the present C₁-symmetry atropo-isomeric ligands are the ligands of formulas (I)c, (I)d, and (I)e represented below:





In the structures (I)c, (I)d and (I)e, Het₁ and Het₂ are defined as Het ; A, B, C, D, E, Q₁, Z₁, P₁, R₁, Q₂, Z₂, P₂, R₂ and T are as defined as for the formula (I) ; m is 0, 1 or 2.

5 Examples of transition metals contained in the organometallic complexes of the present invention are Rh, Ru, Ir, Pt, Pd and Ni.

Construction of the molecular models, conformational analysis, and calculation of the "natural bite angle" were carried out by using the S/W program SYBYL, Version 6.2 [Sybyl; Tripos Associates, 193 S. Hasley Road, Suite 363, St. Louis MO 63144].

Minimisation of the structures, calculation of the energy levels associated to the ground state and to the transition state, and the value of the atomic charges were determined by using the program MOPAC, Version 6.0, Method MNDO [J.P. Stewart, J. Comp. - Aideed Molec. Design, 4 (1), 1990 ; QCPE, Quantum Chemistry Program Exchange - QCMP019 Indiana University - Chemistry Department].

More particularly, the structures of the ligands of formula (I) were created according to step a) of the present procedure by using the SYBYL modelling software, Version 6.2. Then, according to procedures known to the person skilled in the art, a structural investigation was carried out to determine the minimum-energy conformation associated to each individual structure. The reliability of the forecast of the minimum-energy conformer was then increased by subjecting the conformations thus identified to a further structural investigation, defined as

"optimisation", by using the program MOPAC, Version 6.0, method MNDO, via which the energy levels of the conformers were calculated, as well as the values of the residual charge quantities $Q(P_1)$ and $Q(P_2)$ for the phosphorous atoms P_1 and P_2 , and then the $\Delta Q(P)$ as defined above.

5 A further parallel optimisation investigation was carried out, again using the program MOPAC, Version 6.0, method MNDO, to determine the value of the interconversion energy barrier ΔE between the two enantiomers (atropoisomers), or racemisation energy barrier, for each structure of formula (I). This ΔE , as defined above, corresponds to the maximum possible extension,
10 given by the difference between the energy of the maximum-energy conformers E_{trans} and the energy of the minimum-energy conformer E_{min} , for each ligand examined, and was calculated by imposing that the said maximum energy should be the one associated to the conformer in which the two aromatic rings (the two heterocycles, or the heterocycle and the carbocyclic system) are coplanar.

15 For the purposes of the present invention, the cone angle β_n is as defined in the article by Casey et al., *Isr. J. Chem.*, 30, 299-304, 1990, and is determined uniquely by the steric compression of the ligand structure, and not by the valence angle of the transition metal chosen for the complexation. However, it was calculated by using a program other than the software program AMBER which
20 was employed according to the said article.

In fact, according to the present procedure, the cone angle is calculated by using the program SYBYL, Version 6.2, assuming that $M = Rh$ and using the force field parameters of the program TRIPOS, modified by entering the parameters developed for the Rh-diphosphine complexes by M. Kranenburg et al.
25 [*Organometallics*, 14, 3081, 1995]: by means of this modified program, the optimal geometry of the ligand-metal complex was determined, associating the preferred cone angle to the structure of the minimum-energy conformer.

The parameters developed by M. Kranenburg and entered in the TRIPOS force field, which are used in the procedure of the present invention, are given in the
30 following Tables 1-6, in which:

H = hydrogen; Å = angstrom

P.p = phosphorous atom

C.3 = saturated carbon atom (sp^3) bound to the phosphorous

C.ar = aromatic carbon atom bound to the phosphorous

Rh = rhodium; s = single bond; ar =aromatic bond 11

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Table 1

BOND LENGTHS			
Atom i	Atom j	Type of bond	Bond length (Å)
H	P.p	s	1.43
C.3	P.p	s	1.85
C.ar	P.p	s	1.83
Rh	P.p	s	2.315

Table 2

BOND TYPES			
Atom i	Atom j	Type of bond	Ambiguity
H	P.p	s	no
C.3	P.p	s	no
C.ar	P.p	s	no
Rh	P.p	s	no

Table 3

BENDING ANGLE				
Atom i	Atom j	Atom k	Theta	k (Kcal/mol-degrees ²)
H	P.p	H	93.4	0.02
C.3	P.p	H	95	0.02
C.ar	P.p	C.3	96	0.02
Rh	P.p	C.ar	100	0.02
P.p	Rh	P.p	120	0.02
C.ar	P.p	Rh	109.5	0.02

Theta = bending angle between the atoms considered, expressed in degrees

k (kcal/mol-degrees²) = bending force

5

Table 4

STRETCHING ANGLE - Calculation parameters				
Atom i	Atom j	Type of bond	L (Å)	k i,j (Kcal/mol)
C.3	P.p	s	1.85	350
H	P.p	s	1.43	700
C.ar	P.p	s	1.83	1000
P.p	Rh	s	2.315	700

L (Å) = bond length in angstrom

k i,j = stretching force

Table 5

ROTATIONAL BARRIER - Calculation parameters						
Atom i	Atom j	Atom k	Atom l	Type of bond	k (Kcal/mol)	P
*	C.3	P.p	*	s	0.4	3
*	C.ar	P.p	*	s	1	3
*	C.ar	P.p	*	ar	1	3
C.3	P.p	Rh	P.p	s	0.2	3
C.ar	P.p	Rh	P.p	s	0.2	3
C.ar	C.ar	Rh	P.p	s	0.2	3
C.ar	C.3	P.p	Rh	s	0.2	3

k = rotational force

5 P = periodicity

Table 6

Van der Waals radius		
Atom	r (Å)	k (kcal/mol)
P.p	1.8	0.314
Rh	1.844	0.63

r (Å) = Van der Waals radius expressed in angstrom

10 k = Van der Waals force

The chemical synthesis of the phosphorylated ligands according to the present invention is carried out according to one of the following general procedures, in themselves known:

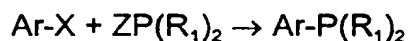
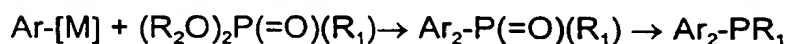
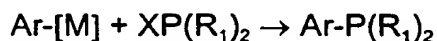
15 A) coupling reaction between aromatic or hetero-aromatic halides with organometallic aryl or hetero-aryl reactants, such as organolithium, organomagnesium, organozinc, organoboron, etc., in the presence of catalytic

quantities of salts or complexes of copper, nickel, or palladium [see, for example, Takao Sakamoto, Yoshinori Kondo, Nobuo Takazawa, Hiroshi Yamanaka, *J. Chem. Soc., Perkin Trans.*, 1, 1996, Pages 1927-1929];

B) cyclisation and aromatisation, with formation of one of the two heterocyclic rings comprised in the structure of formula (I), of a suitable precursor already containing the other heterocyclic or carbocyclic system.

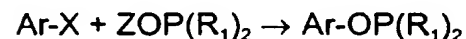
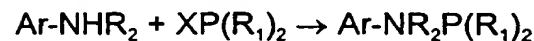
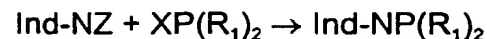
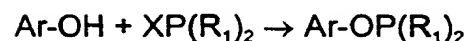
The introduction of the groups containing the phosphorous atom may precede or follow the reaction of formation of the inter-annular bond.

In the case of phosphine derivatives, for example, one of the following reactions in themselves known will be used:



wherein Ar is an aromatic residue comprised in the structure of formula (I) ; [M] is an organometallic group, such as for example Li, MgX, ZnX and an organoboron residue, where X is a halogen ; Z is an alkaline metal, such as Li, Na and K ; R₁ and R₂ are alkyl or aryl residues.

In the case of phosphite or aminophosphine derivatives, for example, one of the following reactions, in themselves known, is used :



wherein Ar is a carbocyclic aromatic or hetero-aromatic residue comprised in the structure of formula (I) ; Ind is an indole residue ; X is a halogen ; Z is an alkaline metal, such as Li, Na and K, or Z is a MgX group ; R₁ is an alkyl or aryl group ; R₂ is H or an alkyl or aryl group.

The resolution of the present phosphorated ligands into their optical antipodes is carried out according to techniques in themselves known; for example, by

separation on chromatographic column or through membrane, by using a chiral stationary substrate or a chiral eluent, or by means of fractioned crystallisation of a corresponding diastereomeric adduct.

If the present phosphorated ligands comprise basic or acidic groups, for example, amine, carboxyl or sulphone groups, the diastereo-isomeric adducts are, for

example, the corresponding salts with enantiomerically pure chiral acids or bases. Alternatively, the diastereo-isomeric adducts may be, for example, the diastereo-isomeric salts among enantiomerically pure chiral acids, and the phosphinoxides

corresponding to the phosphorated ligands, obtained by phosphorous oxidation according to conventional methods : in this case, optical resolution is followed by reduction of the optically active phosphinoxides to phosphine, by means of a treatment with suitable reducing agents, such as sylvans, in non-racemising reaction conditions, for example, according to the procedure described in WO 96/01831.

The preparation of the complexes with transition metals of the present phosphorated ligands is carried out according to techniques in themselves known. The complexes between ligands of formula (I) in the optically active form and transition metals are useful as catalysts in enantio- and/or diastereoselective reactions of reduction, hydroformylation, hydroboration, hydrosilylation, hydrocyanation, allylation, vinylation and other reactions of formation of the C-C bond.

There follow a number of examples given to provide a non-limiting illustration of the present invention.

EXPERIMENTAL PART

Calculation of the parameters of some phosphorated ligands

Applying the procedure of the present invention, the phosphorated ligands having the structures from (1) to (15) illustrated in Figures 1-3, a calculated interconversion energy barrier = 28 Kcal/mole, and the calculated values of $\Delta Q(P)$ and of the natural bite angle according to Casey as given in the following Table 7, have been identified :

Table 7

Compound	$\Delta Q(P)$	Natural bite angle
(1)	0.07	86.7
(2)	0.35	97.3
(3)	0.47	108.6
(4)	0.18	97.1
(5)	0.37	88.3
(6)	0.23	83.7
(7)	0.46	97.5
(8)	0.23	93.3
(9)	0.41	99.7
(10)	0.18	87.3
(11)	0.27	98.7
(12)	0.24	84.4
(13)	0.20	118.8
(14)	0.45	104.1
(15)	0.27	99.3

Preparation of intermediate compounds**EXAMPLE 1****5 Preparation of 3-diphenyl phosphine-2,5-dimethyl-thiophene**

Into a flask, in the following order are introduced : 13.6 ml of water, 4.1 g of sodium iodate, 7.3 g of iodine, 26 ml of acetic acid, 91 ml of ethyl acetate, and 7.8 g of 2,5-dimethyl-thiophene. The mixture is kept under stirring at 25°C, while 3.2 g of 96% sulphuric acid are fed in slowly drop by drop. The mixture is then kept
10 under stirring for 10 hours, cooled down to 15°C, and an aqueous solution of sodium chloride (10 g in 68.5 ml) is added. The aqueous phase is separated, and the organic phase is washed, in order, with an aqueous solution of sodium chloride (10 g in 68.5 ml), an alkaline solution of sodium hyposulphite (6.8 g in 70 ml of 1% sodium hydroxide), and again with an aqueous solution of sodium

chloride (10 g in 68.5 ml). The organic phase is then dried on sodium sulphate and concentrated to yield 16.4 g of crude 3-iodo-2,5-dimethylthiophene. This residue, in inert atmosphere, is treated with 50 ml of DMF, and the following are added: 8.8 g of potassium acetate, 2 mg of palladium acetate, and 13.8 ml of diphenyl phosphine. The mixture is heated up to approximately 130°C and kept at this temperature until the reaction is completed (approximately 15 hours). The mixture is then cooled to approximately 30°C and diluted with 20 ml of water and 300 ml of methylene chloride. The dichloromethylene phase is separated and washed with 30 ml of water. After concentration to dry residue, 18.5 g are obtained of 3-diphenyl phosphine-2,5-dimethyl-thiophene.

EXAMPLE 2

Preparation of 3-dicyclohexyl phosphine-2,5-dimethyl-thiophene

100 ml of a t-BuLi solution 1.5 M in penthane are fed drop by drop, in inert atmosphere and under stirring, into a solution containing 33.1 g of 3-iodo-2,5-dimethylthiophene prepared according to Example 1 and 18.7 g of tetramethyldiamine in 150 ml of THF anhydrous, at -50°C. The temperature of the mixture is made to rise to -20°C in 30 minutes. A solution of chloro-dicyclohexyl-phosphine (36 g) in 40 ml of THF is then fed in drop by drop, and the mixture is kept under stirring while the temperature is brought to 20°C in 4 hours. The mixture is then treated with 50 ml of water and concentrated under vacuum. The residue is treated with 300 ml of methylene chloride. The dichloromethane phase is washed with water (30 ml x 2), then concentrated to residue to yield 28.5 g of crude 3-dicyclohexyl phosphine-2,5-dimethylthiophene. The product is purified by means of silica gel chromatography.

EXAMPLE 3

Preparation of 3-diphenylphosphinyl-4-bromo-2,5-dimethyl-thiophene

Into a flask, in the following order are inserted : 1.5 g of 3-diphenyl phosphine-2,5-dimethyl-thiophene prepared according to Example 1 and 32 ml of methylene chloride. The mixture is kept stirred at -10°C, and at the same time 2.5 g of N-BROMOSUCCINIMIDE are added slowly in portions. The mixture is then kept under stirring for 15 h, at 25°C, then refluxed after addition of a further 1.3 g of N-

BROMOSUCCINIMIDE. After a further 20 h of reaction, 20 ml of water are added, and the phases are separated. The organic phase, re-united to the dichloromethane extract (15 ml) of the aqueous phase, is washed with an aqueous solution of sodium chloride (2 g in 15 ml). The organic phase is then
5 dried on sodium sulphate and concentrated. The residue obtained is purified using silica chromatography to yield 0.9 g of 3-diphenylphosphinyl-4-bromo-2,5-dimethylthiophene.

EXAMPLE 4

Preparation of 3-dicyclohexylphosphinyl-4-bromo-2,5-dimethyl-thiophene

10 Proceeding as in Example 3 and using 1.8 g of 3-dicyclohexyl phosphine-2,5-dimethyl-thiophene instead of 1.5 g of 3-diphenyl phosphine-2,5-dimethyl-thiophene, 1.2 g of 3-dicyclohexylphosphinyl-4-bromo-2,5-dimethyl-thiophene are obtained.

Preparation of phosphorated ligands of the invention

15 EXAMPLE 5

Preparation of (+) and (-) 4-diphenyl phosphine-3-[3'(4'-dicyclohexyl phosphine-2',5'-dimethyl(thienyl))-2,5-dimethyl-thiophene [compound (15)]

A solution of 3-dicyclohexylphosphinyl-4-bromo-2,5-dimethyl-thiophene (3.4 g) prepared according to Example 4 in 20 ml of diethyl ether is fed drop by drop in
20 inert atmosphere into 5 ml of a t-BuLi solution 1.5 M in pentane, at -30°C. The mixture is kept under stirring for 2 h, then 2.5 g of zinc iodide are added to it, and the mixture is allowed to warm up to room temperature. Then a solution of 3-diphenylphosphinyl-4-bromo-2,5-dimethyl-thiophene (3.4 g), prepared according to Example 3, and palladium tetrakis(triphenyl phosphine) (87 mg) in 20 ml of
25 anhydrous tetrahydrofuran is added to it, and the mixture is refluxed until completion of the reaction. The mixture is then treated with 200 ml of water, vacuum-concentrated to a small volume, and the residue treated with 200 ml of toluene; the organic phase is separated and washed with 30 ml of water, filtered on celite and concentrated to yield 2.8 g of crude (\pm) 4-diphenylphosphinyl-3-[3'-
30 (4'-dicyclohexylphosphinyl-2',5'-dimethyl)thienyl]-2,5-dimethyl-thiophene. The product is purified via silica chromatography, and resolved in its optical antipodes

by crystallization of the diastereo-isomeric salts, using enantiomerically pure dibenzoyltartaric acid, for example, according to the procedure described in WO 96/01831. The diastereo-isomerically pure adducts are then unblocked using sodium hydroxide and reduced with trichlorosilane, according to the procedure described in Example 2 of the patent application WO 96/01831, thus yielding approximately 0.7 g of (+) - and (-)-4-diphenyl phosphine-3-[3'(4'-dicyclohexyl phosphine-2',5'-dimethyl)thienyl]-2,5-dimethyl-thiophene.

Alternatively, starting from the racemic diphosphine oxide, the racemic disphosphine is obtained by reduction with trichlorosilane, and is resolved via HPLC on stationary chiral phase.

EXAMPLE 6

Preparation of (+) and (-) 2-diphenyl phosphine-3-[3'(4'-dicyclohexyl phosphine-2',5'-dimethyl(thienyl))-4,6-dimethyl-benzofuran [compound (2)]

A solution of 3-dicyclohexylphosphinyl-4-bromo-2,5-dimethyl-thiophene (3.4 g) prepared according to Example 4 in 20 ml of diethyl ether is fed drop by drop in inert atmosphere into 5 ml of a 1.6 M of t-BuLi solution in penthane at -30°C; the mixture is kept under stirring for 2 h, then 2.5 g of zinc iodide are added to it, and the mixture is allowed to warm up to room temperature. Then a solution of 3-bromo-4,6-dimethyl-benzofuran (1.7 g), prepared according to Example 23 of the patent application WO 96/01831, and palladium tetrakis-triphenylphosphine (57 mg) in 20 ml of anhydrous tetrahydrofuran is added, and the mixture is refluxed until the reaction is completed. The mixture is then filtered on celite and concentrated under vacuum ; the residue is treated with 30 ml of diethyl ether, and the solution, in inert atmosphere, is fed drop by drop into 5 ml of a t-BuLi solution 1.6 M in penthane at the temperature of -30°C ; then 1.4 ml of chlorodiphenyl phosphine is added, and the reaction mixture is allowed to reconstitute at room temperature. After hydrolysis with water, the organic phase is separated and concentrated under reduced pressure; the residue is treated with xylene and reduced with trichlorosilane according to the procedure mentioned previously, to yield 2.5 g of (±) 2-diphenyl phosphine-3-[3'-(4'-dicyclohexylphosphinyl-2',5'-dimethyl)thienyl]-4,6-dimethyl-benzofuran, which is resolved via HPLC on chiral

stationary phase.

EXAMPLE 7

Preparation of (+) and (-) 2-diphenyl phosphine-3-[3'(4'-diphenyl phosphine-2',5'-dimethyl(thienyl))-4,6-dimethyl-benzofuran [compound (1)]

- 5 The procedure of Example 6 is repeated using 3.3 g of 3-diphenylphosphinyl-4-bromo-2,5-dimethyl-thiophene, prepared as described in Example 3, instead of the 3.4 g of 3-dicyclohexylphosphinyl-4-bromo-2,5-dimethyl-thiophene, to recover 2.2 g of racemic 2-diphenyl phosphine-3-[3'(4'-diphenyl phosphine-2',5'-dimethyl(thienyl))-4,6-dimethyl-benzofuran, which is resolved into its optical
10 antipodes by means of HPLC on chiral stationary phase.

EXAMPLE 8

Preparation of (+) and (-) N-diphenyl phosphine-2-[3'(4'-diphenyl phosphine-2',5'-dimethyl(thienyl))-3-methyl-indole [compound (6)]

- To a solution of 4-bromo-2,5-dimethyl-3-propionyl-thiophene (12 g) and
15 phenylhydrazine (34.9) in 250 ml of ethanol are added 61 ml of acetic acid. The mixture is reflux-heated for 4 h, then concentrated under reduced pressure and the residue treated with methylene chloride; the organic phase is washed with a saturated solution of sodium bicarbonate and subsequently with water until neutral pH is obtained. The organic phase is concentrated under vacuum, and the crude
20 reaction product is purified by means of silica chromatography to yield the 4-bromo-2,5-dimethyl-3-propionyl-thiophene phenylhydrazone, which is dissolved in 350 ml of isopropanol/HCl (7.5 M) and kept stirred at room temperature until the reaction is completed. The solvent is removed under reduced pressure, and the residue is treated with methylene chloride. The organic phase is subjected to
25 washings with a saturated solution of sodium bicarbonate, then with water, and finally concentrated under reduced pressure to yield 4.7 g of 2-[3'(4'-bromo-2',5'-dimethyl)-thienyl]-3-methyl-indole.

- Into a solution of 4 g of indole derivative thus prepared in 150 ml of anhydrous diethyl ether and 2.2 ml of N,N,N',N'-tetramethylethylenediamine, cooled to -60°C,
30 16 ml of a t-BuLi solution 1.5 M in penthane are carefully fed in drop by drop. The mixture is allowed to reconstitute at -30°C, and 4.9 ml of chlorodiphenyl phosphine

are added to it. After being kept under stirring overnight at room temperature, the mixture is treated with water and concentrated to a small volume; the residue is treated with 150 ml of methylene chloride, and the organic phase washed with water. The solvent is removed to yield 3.3 g of racemic N-diphenyl phosphine-2-[
5 3'(4'-diphenyl phosphine-2',5'-dimethyl)-thienyl]-3-methyl-indole, which is resolved into its optical antipodes using HPLC on chiral stationary phase.

EXAMPLE 9

Preparation of the complex obtained from [Rh(1,5-COD)₂]ClO₄ and compound (+)(15)

10 In argon atmosphere, equimolar solutions of [Rh(1,5-COD)₂]ClO₄ (COD = cyclo-octadiene) and of the optically pure ligand (+)(15) in dichloromethane are prepared ; these two solutions are then mixed and kept under stirring for 30 minutes. The solution is then concentrated under reduced pressure to yield the Rh complex containing the chiral diphosphine which is used as such without further
15 purification in the enantioselective reduction of olefins. It is assumed that the complex obtained has the following structure:



Using the same procedure, similar complexes of rhodium were prepared with the other optically active phosphines of Table 7.

20 EXAMPLE 10

Preparation of the complex obtained from [Ir(1,5-COD)Cl]₂, compound (+)(15), and tetrabutylammonium iodide

In argon atmosphere, a solution is prepared of toluene/methanol 1/1 (3 ml) containing 2.5×10^{-3} mmol of [Ir(1,5-COD)Cl]₂ and 6.0×10^{-3} mmol of optically pure
25 ligand (+)(15). After 30 minutes, 1×10^{-2} mmol of tetrabutylammonium iodide are added under stirring. The solution thus obtained is used as such without further purification in the enantioselective reduction of imines. It is assumed that the complex obtained has the following structure: [Ir(1,5-COD)(compound (+)(15))]I.

Using the same procedure, similar complexes of iridium were prepared with the
30 other optically active phosphines of Table 7.

EXAMPLE 11

Preparation of the complex obtained from $[\text{Ir}(1,5\text{-COD})\text{Cl}]_2$ and compound (+)(15).

In argon atmosphere, a solution is prepared of diethyl ether (3 ml) containing 2.5×10^{-3} mmol of $[\text{Ir}(1,5\text{-COD})\text{Cl}]_2$ and 5.0×10^{-3} mmol of optically pure ligand (+)(15). After 1 h under stirring, the solution thus obtained is used as such without further purification in the enantioselective hydrosilylation of chetones. It is assumed that the complex obtained has the following structure:

$[\text{Ir}(1,5\text{-COD})(\text{compound (+)(15)})]\text{Cl}$.

Using the same procedure, similar complexes of iridium were prepared with the other optically active phosphines of Table 7.

EXAMPLE 12

Preparation of the complex obtained from $[\text{Ru}(\text{p-cymene})\text{I}_2]_2$ and compound (+)(15).

In argon atmosphere, a solution is prepared of methylene chloride/methanol 8/3 (11 ml) containing 1.6×10^{-2} mmol of $[\text{Ru}(\text{p-cymene})\text{I}_2]_2$ and 3.5×10^{-2} mmol of optically pure ligand (+)(15); after 60 minutes at reflux under stirring, the mixture thus obtained is concentrated under reduced pressure to yield a residue containing the complex, which is used as such without further purification, dissolved in methanol or ethanol, in the enantioselective reduction of carbonyl compounds. It is assumed that the complex obtained has the following structure:

$[\text{Ru}(\text{p-cymene})(\text{compound (+)(15) I})]\text{I}$.

Using the same procedure, similar complexes of ruthenium were prepared with the other optically active phosphines of Table 7.

EXAMPLE 13

Preparation of the complex obtained from $[\text{Rh}(\text{acac})(\text{CO})_2]$ and compound (+)(2)

Into an autoclave in argon atmosphere are introduced a toluene solution (10 ml) containing 2.0×10^{-2} mmol of $[\text{Rh}(\text{acac})(\text{CO})_2]$ and 2.2×10^{-2} mmol of optically pure ligand (+)(2). The autoclave is purged, loaded with CO/H_2 1/1 (pressure, approximately 20 bar) and kept at room temperature for 15 h to form the active catalyst suitable for enantioselective hydroformylation reactions. It is assumed that the complex obtained has the following structure: $[\text{H Rh}(\text{compound (+)(2)})(\text{CO})_2]$.

Using the same procedure, similar complexes of rhodium were prepared with the other optically active phosphines of Table 7.

EXAMPLE 14

Preparation of the complex obtained from NiCl_2 and compound (+)(15)

- 5 A dichloromethane solution (10 ml) containing 4.2 mmol of optically pure ligand (+)(15) is added under stirring to a 4.2 mmol solution of hexahydrated NiCl_2 in 30 ml of ethanol. After 1 h the mixture is concentrated to a small volume, and the residue is squashed with ethanol and subsequently dried under vacuum.

The complex is used as such in enantioselective reactions of formation of C-C
10 bonds. It is assumed that the complex obtained has the following structure:

$[\text{NiCl}_2(\text{compound (+)(15)})]$.

Using the same procedure, similar complexes of nickel were prepared with the other optically active phosphines of Table 7.

EXAMPLE 15

- 15 Preparation of the complex obtained from $\text{PdCl}_2(\text{benzonitrile})_2$ and compound (+)(15)

A dichloromethane solution (10 ml) containing 2.6 mmol of optically pure ligand (+)(15) and 2.6 mmol of $\text{PdCl}_2(\text{benzonitrile})_2$ is kept under stirring for 1 h at room temperature. The mixture is concentrated to a small volume and the residue is
20 squashed with ethanol and subsequently dried under vacuum.

The complex obtained is used as such in enantioselective reactions of formation of C-C bonds. It is assumed that the complex obtained has the following structure:

$[\text{PdCl}_2(\text{compound (+)(15)})]$.

- Using the same procedure, similar complexes of palladium were prepared with the
25 other optically active phosphines of Table 7.